PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JPP462	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2005/000742	International filing date *(day/month/year)* 28.02.2005	Priority date *(day/month/year)* 01.03.2004

International Patent Classification (IPC) or national classification and IPC
INV. A61K9/19 A61K47/00 A61K47/26 A61K47/10 A61K47/36 A61K47/42 A61K39/00 A61K38/00

Applicant
BRITANNIA PHARMACEUTICALS LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.12.2005	09.06.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000742

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
29	as originally filed
Claims, Numbers	
1-14	filed with telefax on 30.12.2005
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,9-14
	No:	Claims	1-3,6-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: WO 02/101412 A, disclosing powders injectable with a needleless syringe and their application e.g. to freeze-dried vaccine compositions
D2: WO 03/030866 A , disclosing freeze-dried preparations of polypeptides with cryo-and lyoprotectant amorphous excipients
D3: US 5 763 409 A , disclosing lyophilized protein formulations with crystalline mannitol and amorphous alanine for assay kits or for administration
D4: WO 01/41800 A , disclosing lyophilised meningococcus C immunogens stabilzed by the addition of at least an amorphous excipient.
D5: US 6 251 599 B1 , disclosing nucleic acid compositions, lyophilized in presence of a zwitterion, a crystalline bulking agent (e.g. mannitol) and an amorphous cryoprotectant (e.g. sucrose)
D6: US 6 586 573 B1 , disclosing a lyophilized factor VIII preparation, stable, albumin-free and with the same ingredients as the present application (amorphous + crystalline)
D7: US 5 874 408 A , disclosing another lyophilised Factor VIII formulation. Stability and freeze-drying properties are a function of the amporphous vs. crystalline contents and of salt concentration; sucrose, trehalose, maltotriose may contribute to the amorphous phase, mannitol to the crystalline one
D8: Izutsu K-I et al: Chemical and Pharmaceutical Bulletin, Pharmaceutical Society of Japan, vol. 42, no. 1, 1994, pages 5-8, disclosing that an amorphous state is important for maintaining lyophilized enzyme activity;
D9: Constantino H R et al: Journal of Pharmaceutical Sciences,
vol. 87, no. 11,(1998), pages 1412-1420, disclosing lyophilisation excipients and their behaviour in the context of crystalline vs amorphous contents of the preparations

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,3,6-8 is not new in the sense of Article 33(2) PCT over

document D1.
D1 explicitely mentions on p. 26, lines 17-22, that the excipients may maintain low hygroscopicity of the powders, and that they can be crystalline or amorphous. Furthermore, on p. 28, first paragraph, D1 states that the most preferred combination includes an amorphous and a crystalline saccharide, the amorphous component being present in amounts between 10 and 90% by weight, which overlaps with said claims.

2. In fact, it is common practice to add excipients which are at least in part amorphous in order to preserve the function of peptidic drugs in freeze-dried preparations. Most of the time exactly the same excipients as in the present preparations are used (sugars, PEGs, povidone, sugar alcohols, saccharides) in different combinations and ratios, see D2-D5.
In the case of novel embodiments, D1 is the closest prior art. The difference is the amount of excipient in amorphous state (the minimum appears to be 10% in D1).The effect appears to be the obtention of a low hygroscopicity.
The only example of the present application where less than 10% of amorphous excipient is present in the dry mass, example 27, does not show any particular effect on the moisture content.
Therefore, no difference appears to be present among the effect of low and high amount compositions (ex. 1-27, last paragraph of the description).
Hence, the problem is to provide an alternative composition with low hygroscopicity.
The use of the compositions suggested by D1 (mixtures of crystalline and amorphous excipient) represents the same solution as the present application.

Moreover, although the low hygroscopicity is not explicitely mentioned in D2-D5, it is considered an inherent problem, when preparing freeze-dried compositions, to maintain the humidity at a low and controlled level while preserving the activity of the drug. That this is in connection with the crystallinity of both the active principles and excipients is widely known (D1-D9), and optimization of the relative amounts of the ingredients is a routine task of the galenic operator.

Hence, the presence of an inventive step under Art. 33(1) and (3) PCT is not acknowledged to present claims 1-14.

3. The patentability of present claims 10 and 11 depends on national law. In some of the Contracting states, preparations containing human embryo cells are excluded from patentability together with their use. Hence, said cells would have to be excluded when the active material is a "whole living cell" or an "eukaryote".

Re Item VIII

Certain observations on the international application

The subject-matter of claim 14 appears to be redundant; the expression "live" is repeated twice in claim 10 (Art. 6 PCT).

CLAIMS

1. Use in a powdered formulation which is a freeze-dried mixture of a sensitive active material and an excipient containing:

from 0.01 preferably from 0.1, more preferably from 0.5 to 50 % by wt of the sensitive active material,

from 50 to 99.99, preferably to 99.9, more preferably to 99.5 % by wt of the excipient,

of at least 0.1 % by wt of the mixture in an amorphous state to substantially reduce the hygroscopicity of the formulation.

2. Use according to claim 1, of from 0.1, preferably from 0.5, more preferably from 1 to 50 % by wt of the freeze-dried mixture in an amorphous state.

3. Use according to claim 1, of:

from 0.01, preferably from 0.1, more preferably from 0.5 to 50 % by wt of sensitive active material in an amorphous state,

from 50 to 99.99, preferably to 99.9, more preferably to 99.5 % by wt of excipient in crystalline state,

0 - 5 % by wt of excipient in an amorphous state.

4. Use according to claim 1, of:

from 0.01, preferably from 0.1, more preferably from 0.5 to 50 % by wt of sensitive active material in a crystalline state,

from 50 to 99.89, preferably to 99.8, more preferably to 99.4 % by wt of excipient in crystalline state, and

0.1 - 5 % by wt of excipient in an amorphous state.

5. Use according to claim 1, of:

from 0.01, preferably from 0.1, more preferably from 0.5 to 25 % by wt of an amorphous or a crystalline state of sensitive active material,
from 75 to 99.49, preferably to 99.4, more preferably to 99 % by wt of a crystalline state excipient, and
0.5 - 5 % by wt of excipient in an amorphous state.

6. Use according to any of claims 1 to 5 in which a saccharide is used to provide an excipient in an amorphous state.

7. Use according to any one of claims 1 to 5 in which a sugar alcohol is used to provide an excipient in a crystalline state.

8. Use according to any one of the preceding claims wherein the formulation additionally contains from 0.1 to 10% by wt (preferably from 1 to 10% by wt) of additive/stabilizer.

9. Use as defined in claim 8 wherein the additive/stabilizer is an antioxidant, a free radical scavenger and/or a Maillard reaction suppresser.

10. Use according to any one of the preceding claims wherein the sensitive active material is a labile organic and/or inorganic molecule, a biopolymer, a polypeptide, protein, enzyme, hormone, vitamin, antibiotic, polysaccharide, lipid, killed or live whole live cell.

11. Use according to claim 10 wherein the sensitive active material is a virus (including phage), bacterium, fungus and/or eukaryote.

12. Use according to any one of the preceding claims of a stable crystalline/amorphous matrix.

13. Use according to any one of the preceding claims which substantially reduces the hygroscopicity of the formulation to a hygroscopicity of less than 5% by weight, preferably less than 3% by weight, more preferably less than 2% by weight, wherein the hygroscopicity is measured by the percentage increase in the weight of the formulation after 8 hours in a 75% relative humidity environment.

14. Use according to any one of the preceding claims substantially as hereinbefore described.